UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/796,164	02/06/97	STAMLER	[illegible]

HM12/0731

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EXAMINER	
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ART UNIT	PAPER NUMBER
1627	

DATE MAILED: 07/31/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

File copy

Office Action Summary

Application No.	Applicant(s)
08/796,164	Stamler et al.
Examiner	**Group Art Unit**
Bennett Celsa	1627

☒ Responsive to communication(s) filed on *May 8, 2000*.

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *10-22, 24-29, 40, 41, 43, 44, 46, 63, 65, and 66* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *10-22, 24-29, 40, 41, 43, 44, 46, 63, 65, and 66* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- *SEE OFFICE ACTION ON THE FOLLOWING PAGES* ---

DETAILED ACTION

Response to Amendment

Applicant's amendment dated 5/1/00 in paper no. 30 is hereby acknowledged.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status Of The Claims

Claims 10-22, 24-29, 40, 41, 43, 44, 46 and 63, 65 and 66 are currently pending and under consideration.

Withdrawn Objection(s) and/or Rejection (s)

The new matter rejections of claims 64, 67 and 68 have been rendered moot in view of applicant's cancellation of these claims.

Similarly, the rejection of claims 45 and 68 as indefinite has been rendered moot in view of applicant's cancellation of these claims.

Further in this regard, the anticipation rejection of claims 42 and 45 over the Moore et al., and Sharma et al. references have been rendered moot in view of applicant's cancellation of these claims.

Outstanding Objection(s) and/or Rejection (s)

2. Claims 63 and 65-66 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention (e.g. NEW MATTER REJECTION)

The specification disclosure (bottom of page 72-top of 73) of a specific multistep protocol for forming SNO-Hemoglobin does not support the generic method **claim 63.**

The specification disclosure (bottom of page 75- top of page 76) which discloses a specific multistep protocol for making SNO-Hb which includes specific buffer and amounts does not support the generic method of new **claim 65.** Additionally, there is no support for the newly added language (e.g. 5/1/00 amendment) e.g. "at a heme:NO ratio of less than about 10".

Similarly, specific support for 18.3uM hemoglobin fails to support the range of "greater than about 18uM" in dependent **claim 66.** Additionally, there is no support for the newly added language (e.g. 5/1/00 amendment) e.g. "at a heme:NO ratio of less than about 100".

A response to this rejection must include cancellation of the newly added subject matter.

Discussion

Applicant's arguments directed to the above modified new matter rejection were considered but deemed nonpersuasive for the following reasons.

Initially, it is noted that the above rejection was revised to address newly amended (e.g. 5/1/00 amendment) claim limitations.

Regarding claim 63, Applicant argues that the claim limitations contain all of the necessary "essential" features and "one of ordinary skill in the art would need no further instruction".

However, to the extent that applicant is arguing that the presently claimed (e.g. claim 63) invention is "enabled" such an argument is NOT persuasive with regard to a new matter rejection which is addressed e.g. inadequate written description. Applicant's claim is clearly MUCH broader than the disclosed "hypothetical" example and accordingly, and as such, is clearly not supported by the specification example which defines specific reaction parameters not present in the presently claimed invention.

Turning to the newly amended claims 65 and 66, the newly specified ratio limitations lack specification suport and thus constitute new matter. Applicant must specifically point out where in the specification provides specific or representative support for demonstrating possession for the presently claimed ratios.

Accordingly, the above modified new matter rejection is hereby retained.

3. Claims 10-15, 46, 63, 65 and 66 are rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling.

Critical or essential method parameters: which include reagent concentration, pH and presence and concentration of buffer, necessary to the practice of the invention, but not included in the claim(s) is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976).

For instance the specification specifically states on page 77, lines 25-30 that "... the balance between oxidation and nitrosothiol formation is dependent upon the ratio of nitric oxide to hemoglobin and the buffer environment. Accordingly, **both** buffer presence in effective amounts and NO: heme concentrations are critical to practicing the presently claimed methods and the achieving of the presently claimed compositions.

Similarly, specification pages 73-74 disclose that NO:heme ratios and whether the method is performed under anaerobic or aerobic conditions are critical since different ratios and atmospheric conditions result in different final products (e.g. in site and degree of nitrosylation and degree of oxidation).

Finally, the submitted Stamler Declaration provides further evidence that the choice of nitrosating agent, the amount of agent vis a vis hemoglobin concentration, and pH are critical toward obtaining stable S-nitrosylation of hemoglobin.

Discussion

Applicant's arguments directed to the above "modified" enablement rejection were considered but deemed nonpersuasive for the following reasons.

Initially it is noted that the above rejection was modified to remove cancelled claims 42, 45, 64, 67 and 68 from the scope of rejection coverage.

With regard to the composition claims 10 and 13, it is noted that the term "comprising" would read on a "soup" (e.g. a mixture of other undesired byproducts in addition to the desired S-nitrosylated hemoglobin). To be consistent with the Stamler Declaration evidence of record as

discussed above; the above nonenablement rejection will be applied to the composition claims (e.g. claims 10 and 13) unless and until applicant amends to recite "consisting essentially of" for "comprising" in order to more accurately conform to Declaration showing of obtaining y recite S-nitrosylated hemoglobins without detectable Fe heme oxidation which is absent of undesired contaminants.

In response to the above ESSENTIAL subject matter enablement rejection with respect to the method claims applicant argues that the specification adequately describes "operable" reaction parameters (e.g. various ratios of reagent to hemoglobin) and an assay that can be used to detect SNO hemoglobin.

However, applicant fails to address the crux of the above enablement rejection which cites supporting case law for the proposition that *essential* method parameters (and even compound parameters) MUST be recited in the claim. Applicant's own specification and proferred Declaration evidence specifically supports the essential nature of the presence of a buffered pH environment and the further requirement of critical NO:heme ratios which are necessary to arrive at S-nitrosylated hemoglobin without detectable oxidation of the heme Fe which is argued by applicant to distinguish over the prior art references; including applicant's own reference (argued to be nonenabled for lack of the critical claim parameter e.g. concentration and pH to name a few).

Accordingly, the above enablement rejection, as modified, is hereby retained.

4. Claims 10-14, 43, 44, 63, 65 and 66 are rejected under 35 U.S.C. 102(b) as being anticipated by or alternatively under 35 USC 103 as being obvious over Wade and Castro, Chem. Res Tox. 1990 Vol. 3, pages 289-291.

The reference discloses a method of transferring the nitrosyl group to sulfur (as well as oxygen, nitrogen and sulfur) of heme proteins, including hemoglobin to thus form SNO-hemoglobin by reacting hemoglobin in pH 7.4, 0.01 buffer (see table 1) under anaerobic conditions in excess nitric oxide (e.g. @ 2x10-3M) (e.g. see page 289 under "Results and Discussion").

The reference NO and hemoglobin concentrations are within the scope of the presently claimed invention. It is noted that a "composition" comprising an S-nitrosylated hemoglobin in which additionally other moieties (e.g. carbon, oxygen and nitrogen) are within the scope of the present composition claims. The isolation of the nitrosated hemoglobin species and/or the spectrophotometric determination (e.g. page 290) presumably in air would be expected to form the the oxyhemoglobin species. Alternatively, it would have been obvious to one of ordinary skill in the art to generate the oxygenated hemoglobin species by air oxidation especially since the reference specifically points to a nitrosation process which occurs under aerobic conditions.E.g see page 290, left column and footnote 4. The degree of heme oxidation (e.g. "nondetectable") of the reference nitrosylated hemoglobin would be met inherently by the reference which utilizes a method within the scope of the presently claimed invention. The Examiner lacks the facilities to do testing.

Discussion

Applicant's arguments directed to the above 102/103 rejection were considered but deemed nonpersuasive for the following reasons.

In essence applicant argues that the Wade and Castro reference fails to teach that the reference reaction conditions produce S-nitrosylated hemoglobin without detectable oxidation of the heme Fe.

As recited in the above rejection, the method steps and reagents as presently claimed are specifically taught by the reference. The reference also discloses and suggests S-nitrosylation of hemoglobin. Accordingly, S-nitrosylation "withhout detectable oxidation of heme Fe" must result (inherently or otherwise) since the reference is practicing the SAME METHOD STEPS as presently claimed. Applicant should consider amending the claims to recite claim parameters which distinguish over the reference method.

With regard to the composition claims it is noted that "comprising" is open ended. Since the reference method meets the presently claimed method limitations a composition within the scope of the presenlty claimed invention must result. Applicant may consider amending to recite "consisting essentially of" or "consisting of" which would be more consistent with applicant's arguments and Declaration evidence (e.g. by Dr. Stamler and others) of record.

Accordingly, the above rejection is hereby retained.

5. Claims 16, 20-22, 27-28 and 40 are rejected under 35 U.S.C. 103(a) as obvious over Stamler et al, WO 93/09806 (5/93).

Stamler et al. teach that nitrosylated low molecular weight thiols (e.g. N-acetyl cysteine) serve as NO donating compounds (e.g. delivery of NO) which are therapeutically useful as smooth muscle relaxants, vasodilators and platelet inhibition (e.g. see abstract and pages 1-2 of Stamler).

Similarly to low molecular weight thiols, the Stamler reference further teaches that proteins (including hemoglobin), which are nitrosylated on oxygen, carbon or nitrogen sites possess the same therapeutic utility as nitrosylated/nitrated low molecular weight thiol compounds. (E.g. see page 6, lines 13-15; page 7, lines 17-21; and claims).

The reference specifically discloses the use of nitrosylated proteins and low molecular weight nitrosating agents (e.g. see pages 1-2; page 24, lines 10-16) preparations thereof for the treatment of disorders by increasing oxygen capacity and transport; modulating CO and NO to tissues; scavenging radicals and vasodilation such as treating lung diseases (e.g. ARDS) and hypoxic disorders (E.g. see pages 19-25 and claims).

Further it is known in the art that hemoglobin is involved in regulating oxygen metabolism by its ability to bind reversibly to blood oxygen and thus facilitate the capability of blood to transport oxygen to bodily tissues (e.g. see bottom of page 19-top of page 20).

Accordingly, it would have been obvious to combine a low molecular weight thiol or nitrosothiol with either hemoglobin or nitrosated hemoglobin to deliver oxygen or NO (e.g. claim

16) since the Stamler reference teaches the use of the same compounds separately to effectuate the same function.

Additionally, the use of Nitrosated/Nitrated proteins, including nitrosated/nitrated hemoglobin to deliver NO to tissues (e.g. claim 40) in order to effectuate the treatment of abnormalities or diseases which are mediated by nitric oxide and oxygen metabolism (e.g. lung disease, sickle cell anemia, heart disease, high blood pressure etc.) would have been obvious since the reference discloses the use of nitrosated proteins, including nitrosated hemoglobin, to treat such disease states.

6. Claim 41 is rejected under 35 U.S.C. 103(a) as being unpatentable over Stamler WO93 as applied to claims 16, 20-22, 27-28 and 40 above, and further in view of Moore et al., J.Biol. Chem. Vol. 251, No. 9, (5/76) pages 2788-2794 or Sharma et al., J. Biol. Chem. Vol. 253, No. 18 (9/78) pages 6467-72.

The Stamler reference disclosure discussed in the above obviousness rejection over Stamler alone is hereby incorporated by reference in its entirety.

The Stamler reference although disclosing the use of nitrosyl-heme containing NO donors to deliver NO or its biological equivalent to tissues (e.g. present claim 40) fails to specifically disclose the use of nitrosylhemoglobin (e..g dependent claim 41)..

However, nitrosylhemoglobin compositions are conventionally known in the art. E.g. See the Moore and Sharma references.

One of ordinary skill in the art would be motivated to selected nitrosylhemoglobin to deliver NO to tissues in view of the Stamler reference which suggests that this compound would be expected to function as an NO-donating compound.

Accordingly, it would be obvious for one of ordinary skill in the art at the time of applicant's invention to select available nitrosylhemoglobin compositions to deliver NO as taught by Stamler.

7. Claims 10-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stamler (WO 93).

The presently claimed invention is directed to producing a composition comprising either SNO-Hb[FeII]O2 (produced in the presence of oxygen) or SNO-Hb[FeII] (produced in the absence of oxygen) by reacting "excess nitrosating agent" with purified hemoglobin (e.g. claims 10-11 and 13-14). Claims 12 and 15 specifically select a low molecular weight S-nitrosothiol as the nitrosating agent.

Stamler discloses different methods for thiol nitrosylation of proteins (as disclosed on page 30-31) which include:

1. reaction of nitrosylating agent (e.g. equimolar amounts of acidic NaNo2 as nitrosating agent in a buffered saline at pH 7.4 for tPA);

2. exposure of the protein (e.g. tPA to NO gas in buffered saline)

With regard to the above, Stamler further notes that other oxides of nitrogen can be utilized (e.g. NOCL, N2O3) as well as other nitroso equivalents.

However, the above two reference methods for thiol nitrosylation fail to disclose the use of "excess" nitrosating agent, and preferably the selection of a low molecular weight S-nitrosothiol as the nitrosating agent for thionitrosylation of hemoglobin.

But the Stamler reference (e.g. Example 19 on pages 58-59) specifically discloses the preferential selection of a low molecular weight S-nitrosothiol (e.g. SNOAC) instead of acidic Na NO2 as utilized for tPA due to reduced ability of the SNOAC as compared with acidic nitrate to bind at the redox metal which reduces oxygen binding affinity.

Further, the use of "excess nitrosating agent" in either reaction 1. or 2 above is suggested by the Stamler reference since providing a greater concentration of NO serves to enhance the therapeutic efficacy of the nitrosylated proteins (e.g. see bottom of page 23-top of 24)

It is further noted that the use of higher pH values (e.g. pH 7.4) than that utilized in the thionitrosylated hemoglobin example (e.g. pH 6.9 Example 19) is also suggested by the reference since thionitrosylated proteins are known to be stable under physiological conditions (e.g. TBS, pH 7.4, room temperature: see page 31) and further the reference discloses the use of pH7.4 in the steps analogous to that of Example 19: see page 30, lines 20-27; page 33, lines 20-26).

Optimization of reaction conditions is within the skill of the art.

Additionally, it is a matter of obvious design choice to select anaerobic conditions for making a deoxygenated hemoglobin derivative and aerobic conditions when desiring to make an oxygenated hemoglobin derivative.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time of applicant's invention to synthesize thionitrosylated hemoglobin by using "excess" nitrosating agent, and preferably a low molecular weight S-nitrosothiol, and to further optimize pH during nitrosylation to utilize physiological conditions to form a more stable nitrosylated oxy/deoxy hemoglobin.

8. Claims 17-19 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Feola et al. , U. S. Pat. No. 5,439,882 (8/95: filed 5/93 or earlier) and Stamler, and if necessary further in view of Moore or Sharma.

Feola et al. disclose the state of the prior art regarding "blood substitutes" as being an emergency resuscitative fluid that:

a. Restores blood volume;

b. Transports oxygen;

c. Reduces vasoconstiction. See Feola col. 1.

Feola et al. disclose the use of "blood substitutes" which comprises hemoglobin alone or combined with glutathione as a blood substitute to treat blood disorders (e.g. sickle cell anemia) (e.g. see Abstract, examples and columns 1 and 7).

The Feola reference "blood substitute" composition and intended use thereof (e.g. treat sickle cell anemia) differs from the presently claimed invention which utilizes nitrosated hemoglobin alone or with a low molecular weight S-nitrosothiol instead of hemoglobin or hemoglobin combined with glutathione.

However, Stamler et al. teach that nitrosylated low molecular weight thiols (e.g. N-acetyl cysteine) serve as NO donating compounds (e.g. delivery of NO) which are therapeutically useful as smooth muscle relaxants, **vasodilators** and platelet inhibition (e.g. see abstract and pages 1-2 of Stamler).

The Stamler reference specifically discloses the use of nitrosylated proteins and low molecular weight nitrosating agents (e.g. see pages 1-2; page 24, lines 10-16) preparations thereof for the treatment of disorders by increasing oxygen capacity and transport; modulating CO and NO to tissues; scavenging radicals and vasodilation such as treating lung diseases (e.g. ARDS) and hypoxic disorders (E.g. see pages 19-25 and claims).

Thus, the Stamler et al. reference provides the skilled artisan with motivation to utilize nitrosated hemoglobin alone or with a low molecular weight S-nitrosothiol to make a blood substitute for treating sickle cell anemia in order to increase blood volume, oxygen delivery and reduce vasoconstriction as effected by nitrosated hemoglobins alone or in conjunction with a nitrosothiol.

Further, nitrosylated hemoglobin preparations, e.g. nitrosylhemoglobin compositions, are conventionally known in the art. E.g. See the Moore and Sharma references.

Accordingly, it would have been obvious to the skilled artisan at the time of applicant's invention to make a blood substitute comprising nitrosated hemoglobin alone or in conjunction with a low molecular weight nitrosothiol for their expected benefits as suggested by the Stamler reference and in analogous manner as the Feola reference composition..

9. Claims 24-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Feola et al. and Stamler, and if necessary further in view of Moore or Sharma.as applied to claims 17-19 and 26 above, and further in view of Chem. Res Tox. 1990 Vol. 3, pages 289-291.

As discussed above, and as hereby incorporated by reference in its entirety, the Stamler reference suggest the use of nitrosylated hemoglobin alone or combined with a thio containing compound in order to function equivalently to the Feola hemoglobin preparation as a blood substitute useful to treat sickle cell anemia.

Claims 24-26 are drawn to the use of a thionitrosylated hemoglobin as the nitrosating agent to be employed in the blood substitute.

However, S-nitrosylation of hemoglobin serves to increase hemoglobin-oxygen binding as taught by Stamler et al. (E.g. see pages 19-20).

Additionally, Stamler discloses different methods for thiol nitrosylation of proteins (as disclosed on page 30-31) which include:

1. reaction of nitrosylating agent (e.g. equimolar amounts of acidic NaNo2 as nitrosating agent in a buffered saline at pH 7.4 for tPA);

2. exposure of the protein (e.g. tPA to NO gas in buffered saline)

With regard to the above Stamler further notes that other oxides of nitrogen can be utilized (e.g. NOCL, N2O3) as well as other nitroso equivalents.

Specifically with regard to hemoglobin, Stamler further discloses (e.g. Example 19 on pages 58-59) the preferential selection of a low molecular weight S-nitrosothiol (e.g. SNOAC) instead of acidic Na NO2 and provides motivation to utilize "excess nitrosating agent" in either reaction 1. or 2 above in order to enhance the therapeutic efficacy of the nitrosylated proteins (e.g. see bottom of page 23-top of 24). Optimization by using higher pH values (e.g. pH 7.4) than that utilized in the specific thionitrosylated hemoglobin example (e.g. pH 6.9 Example 19) is also suggested by Stamler since thionitrosylated proteins are known to be stable under physiological conditions (e.g. TBS, pH 7.4, room temperature: see page 31). See also other Examples which utilize physiological conditions in analogous steps.E.g. page 30, lines 20-27; page 33, lines 20-26).

Further, the Chem. Res Tox. 1990 Vol. 3, pages 289-291 discloses a method of transferring the nitrosyl group to sulfur (as well as oxygen, nitrogen and sulfur) of heme proteins, including hemoglobin to thus form SNO-hemoglobin; and thus form thionitrosylated hemoglobin compositions. .

Accordingly, it would have been obvious to one of ordinary skill in the art at the time of applicant's invention to use thionitrosylated hemoglobin as the nitrosating agent to be employed

in a blood substitute in view of the benefits flowing therefrom e.g. enhanced oxygen binding as disclosed by the Stamler reference.

Discussion

Applicant's arguments directed to the above rejections were considered but deemed nonpersuasive for the following reasons.

Applicant argues that the Declaration evidence (e.g. by Dr. Stamler) is sufficient to overcome the above rejections of record.

Applicant's arguments are clearly not commensurate in scope to the claimed invention which is not specifically limited to compositions which "consist essentially of" S-nitrosylated hemoglobin w/o detectable oxidation of the heme to which the Declarant evidence establishes the nonenablement of the Stamler reference to produce. Simiarly, the claimed methods of making are not commensurate in scope to applicant's arguments since these claims are considerably broad so as to encompass prior art methods of making nitrosylated hemoglobin. Similarly, the method of use claims are not so limited to the use of " S-nitrosylated hemoglobin w/o detectable oxidation of the heme.

Applicant's argument that prior to the present invention, the NO donor activiity of nitrosated hemoglobins was not known is specifically rebutted by the WO 93/09806 reference which specifically teaches the reaction of low molecular weight thiols with various proteins, including hemoglobin, to form NO-donating compounds (e.g. see WO 93/09806 abstract and page 1).

Applicant's argument of the Moore et al. And Sharma et al. reference taken alone (e.g. as not teach NO donation of nitrosylated/nitrosated hemoglobins) is not persuasive since the teaching of this reference is combined with WO 93.09806 reference which suggests the ability of nitrosylated/nitrosated proteins (e.g. hemoglobin) to act as NO donors.

Similarly, applicant's arguments directed to the Stamler reference (WO 93/09806) taken alone (e.g. claims 10-15) was considered but deemed nonpersuasive.

Applicant argues that th Stamler reference methods as disclosed on pages 30-31 would fail to produce S-nitrosylated hemoglobin.

However, the scope of applicant's claims are NOT limited to S-nitrosylated hemoglobin (w/o detectable heme oxiiation) but are generically drawn to nitrosylated/nitrated hemoglobin to which the Stamler reference teaches can be used in an NO donating capacity (e.g. See Stamler reference pages 1-4).

To the extent that applicant is arguing that only S-nitroslated hemoglobins can be used as NO donors; such an argument is inconsistent with the presently claimed invention which is not so limited nor is such an argument consistent with the Stamler WO 93 reference which suggests otherwise.

Applicant's arguments regarding the criticality of NO-heme ratios; pH are not persuasive since such arguments are not commensurate to the presently claimed invention.

Applicant argues that the recitation of "if necessary" in the preamble requires clarification.

The term "if necessary" is being used in the same nature as the term "alternatively" which is believed to be consistent with content of the obviousness rejections recited above.

Accordingly, the above rejections are hereby retained.

Allowable Subject Matter

In order to expedite the allowance of this and related applications the following guidance is offered by the examiner:

Compositions should be commensurate to the Declaration evidence: e.g. "consisting essentially of" S-nitrosylated hemoglobin w/o detectable oxidation of the heme. Methods of using these specific compositions would necessarily be novel and unobvious. Finally, the method claims should contains those essential limitations necessary to achieve the above compositions.

Additionally, related applications should be similarly addressed and if necessary claims amended and/or cancelled in order to address potential double patenting rejections which only serve to delay patent issuance.

Please contact the examiner if further assitance is necessary to expedite the allowance of this and the other related applications.

Double Patenting

10. Claims 10-22, 24-29, 40, 41, 43, 44, 46 and 63, 65 and 66 of this application conflict with claims which are present in Application No.08/667,003 and 08/796,164. 37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of

good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822.

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

General information regarding further correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Celsa whose telephone number is (703) 305-7556.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jyothsna Venkat (art unit 1627), can be reached at (703)308-0570.

Any inquiry of a general nature, or relating to the status of this application, should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Bennett Celsa (art unit 1627)

July 28, 2000

BENNETT CELSA
PRIMARY EXAMINER